In Vitro & CFD Bioequivalence Testing for Orally Inhaled Drug Products

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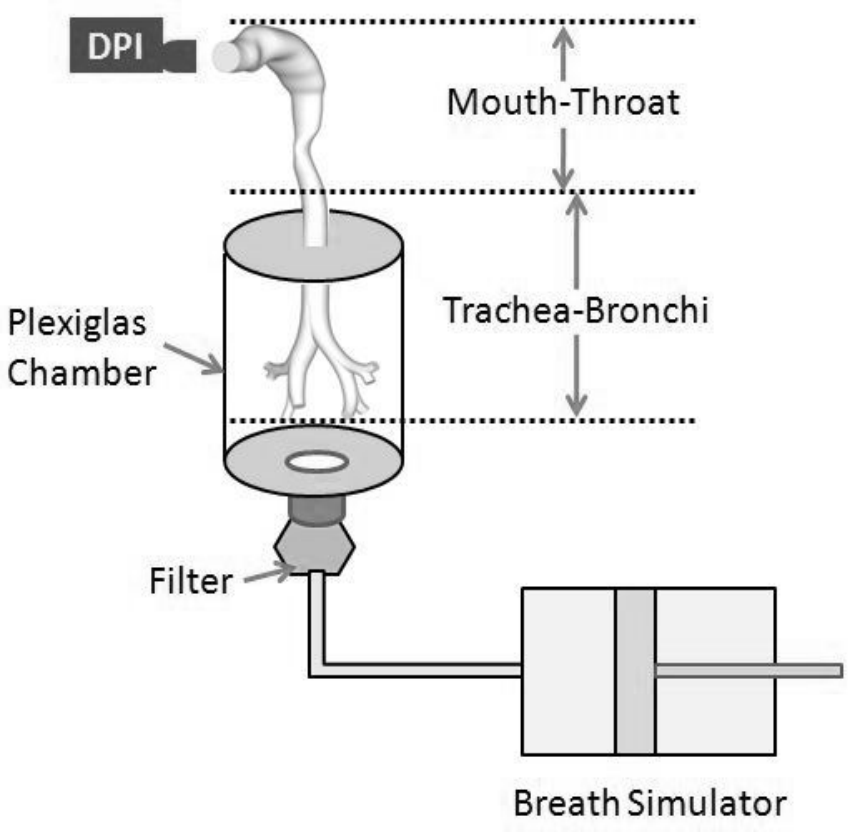
Based on a belief that 2 inhalers should be "BE" when their drug deposition in lung occurs in the same form, doses and locations… "*we set out to research [biorelevant in vitro and CFD] methods to partner realistically-designed airway models with representative inhalation profiles, so that …proving drug deposition equivalence was facilitated….*"

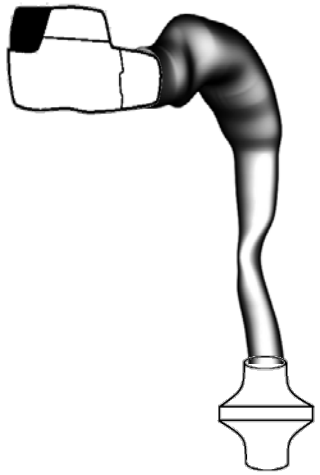
Peter Byron, 2010.

Where are we now and what should we do to move forward?

Biorelevant Test Methods

VCU Pharmacy





VCU Mouth-Throat Model (RDD 2010)

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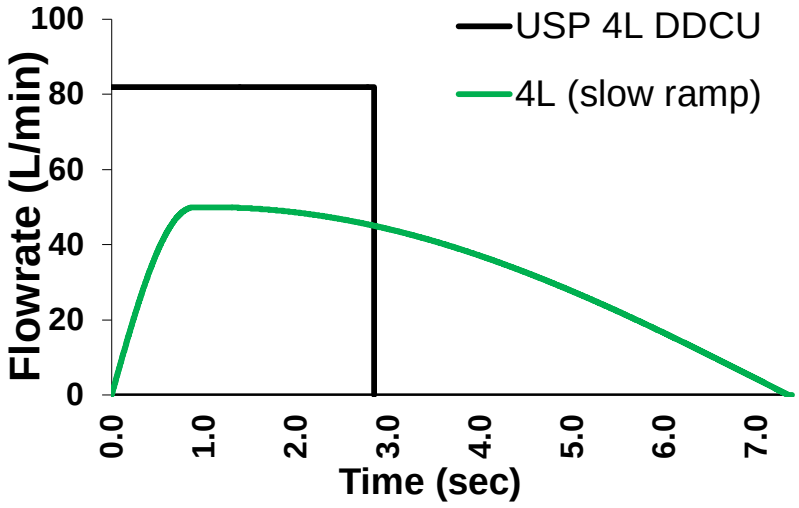


- ❑ Realistic geometries
- ❑ Internal surfaces coated
- ❑ Realistic airflow profiles
- ❑ Total Lung Dose in vitro = $TLD_{in\ vitro}$ = Drug mass escaping MT

Outline

- **New method development**
  - VCU's 2010 model was "hypothetically medium - sized"
  - "Large" and "small" models developed and paired with "simulated, realistic, inhalation profiles"
    - Models validated "geometrically"- anatomy literature
    - Results from "*in vitro* methods" compared to deposition data in literature from trained humans.. ***IVIVC***
- **Choosing the inhalation profiles**
  - Realistic ranges for DPI inspiratory maneuvers
- **Predicting regional lung deposition based on aerosol properties of $TLD_{in\ vitro}$ (use of validated CFD)**
- **The future**

New Method Development and IVIVC - Scaled MT-TB models for normal human adults

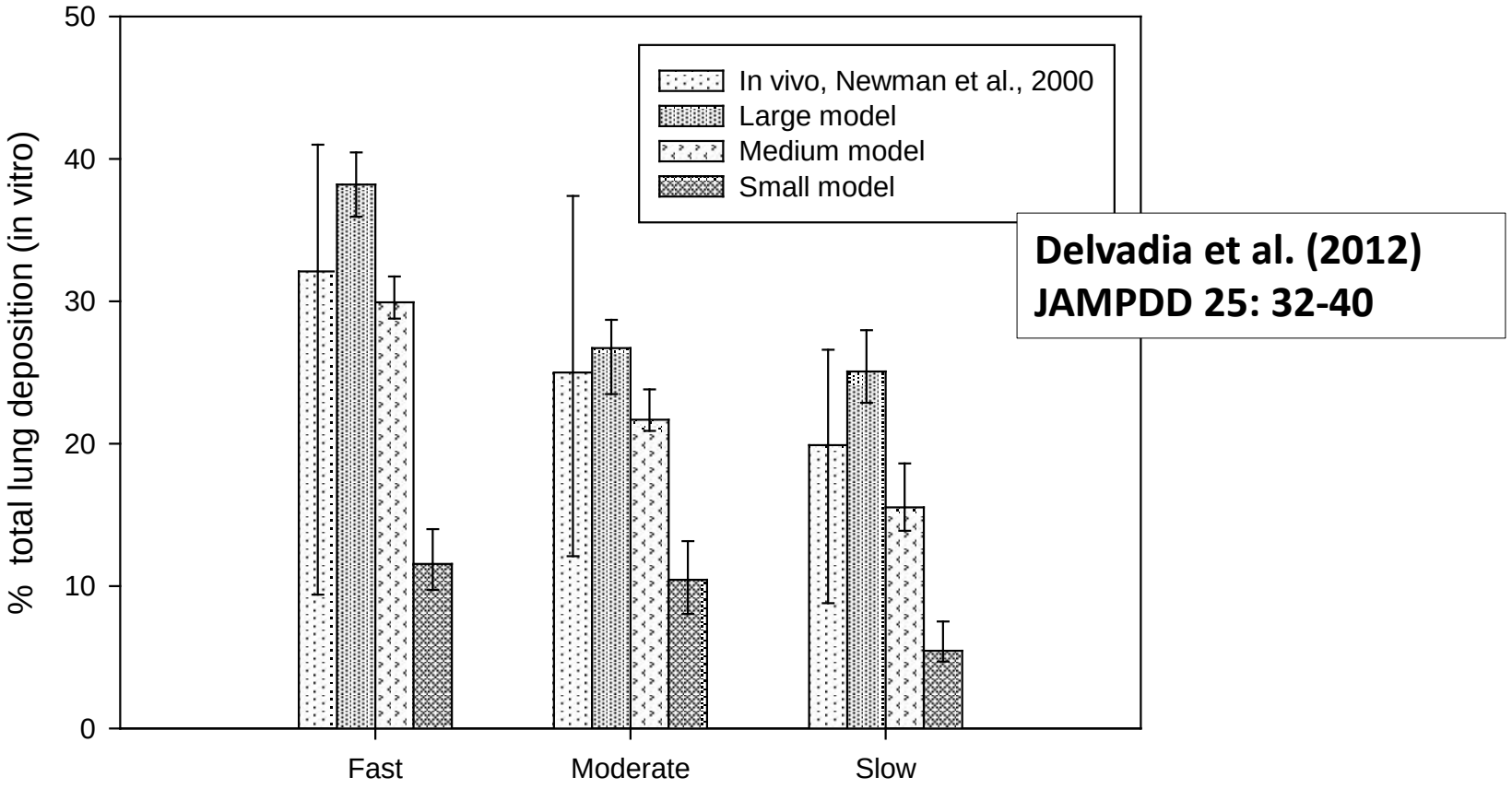
- "VCU Medium" MT model scaled by volume ± 2 SD from literature
  - S =27.2, M = 65 ; L = 107.8 cm^3
- Same scaling factors used for TB
- This normal distribution of volumes appears consistent with anatomy literature & linear scaling factors
  - Length x 0.748 = small
  - Length x 1.0 = medium
  - Length x 1.165 = large

…models shown at left

www.rddonline.com/resources/tools

- MT designed to accept inhaler mouthpiece adapters

Budelin Novolizer: $TLD_{In\ Vivo}$ vs $TLD_{In\ Vitro}$



Delvadia et al. (2012)
JAMPDD 25: 32-40

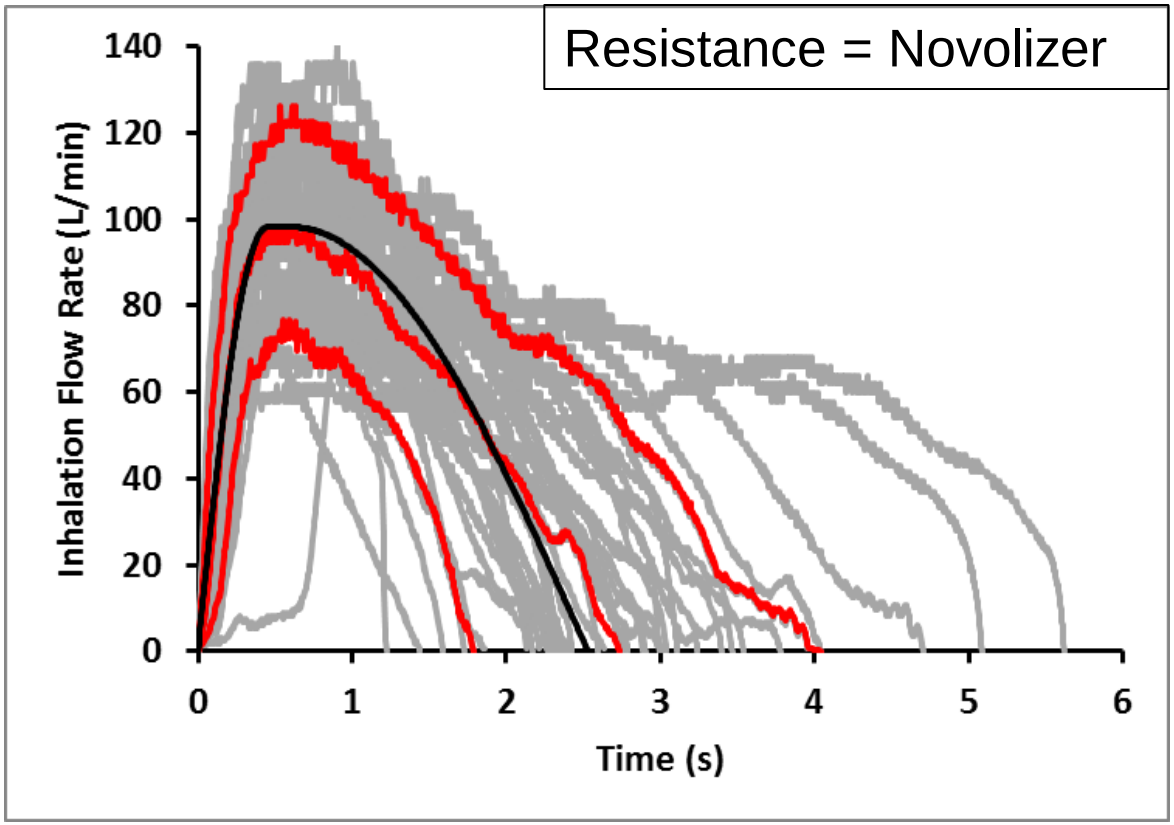
- In vivo results - gamma scintigraphy [Newman, Eur. Resp. J. 16: 178]
- IVIVC from 3 models – flow profiles simulated to match Newman
- Error bars = entire range(all cases)

Summary

- Median & range of $TLD_{in\ vivo}$ correlates with $TLD_{in\ vitro}$
  - when simulated flow extremes coupled with upper airway geometry extremes for a mixed gender, adult population.
  - Statistically significant differences between S, M and L model correlations (Budelin Novolizer)
- Median $TLD_{in\ vivo}$ also correlates with $TLD_{in\ vitro}$ in VCU_{medium} model for Handihaler (tiotropium + lactose), Aerolizer (formoterol + lactose), Easyhaler (albuterol + lactose), Turbohaler (terbutaline)
  - Delvadia et al, JAMPDD 2013, 26: 138 - 144
- Product comparisons best performed with inhaler - representative breath profiles
- Need to determine how ***$TLD_{in\ vitro}$*** deposits regionally.

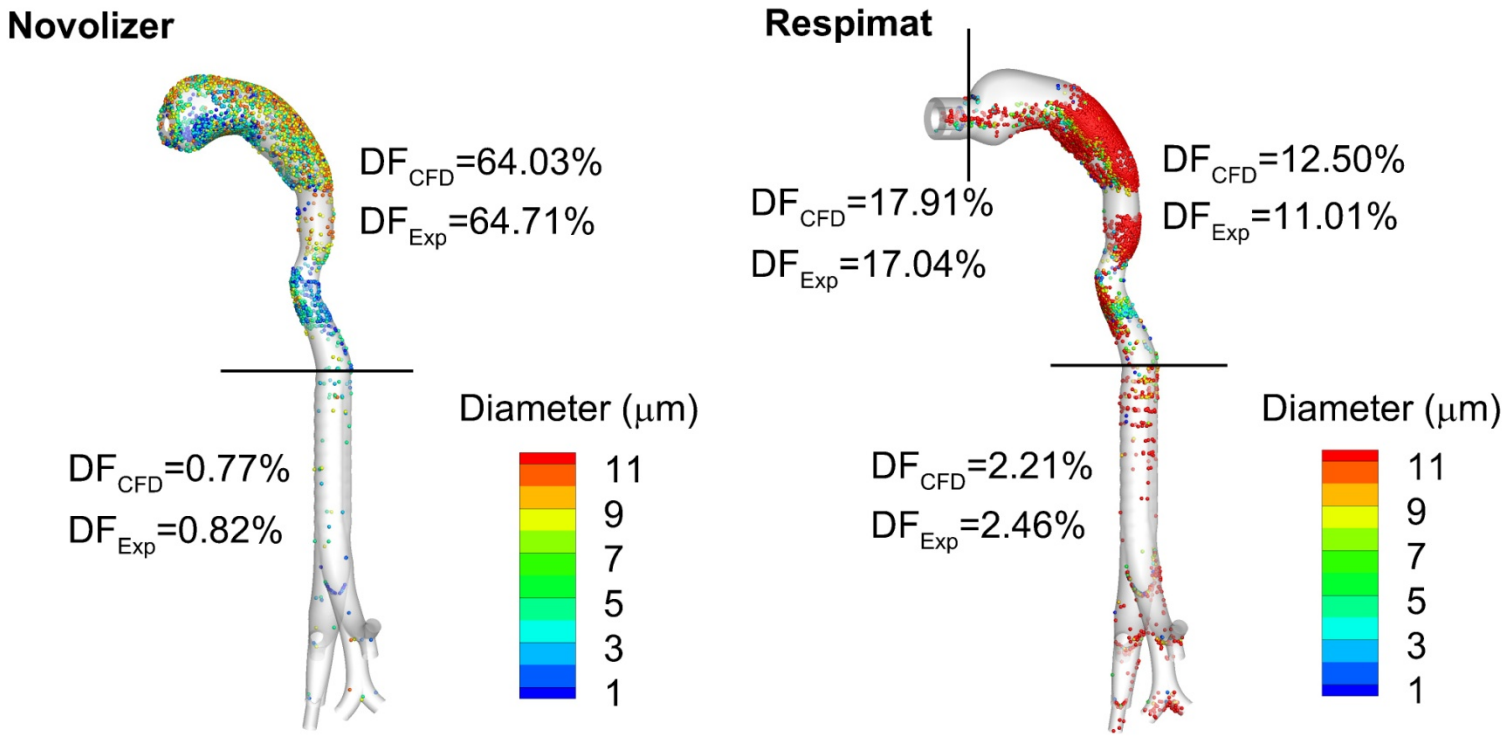
Profile Analysis – toward standard profiles

- Normal profiles, across resistances, DPI trained, 20 adult volunteers
- Gray profiles = Flow rate from mouthpiece
- **Red** profiles = 10, 50 and 90 percentiles
- **Black** = sine wave curve-fit to 50% profile (breath simulator)



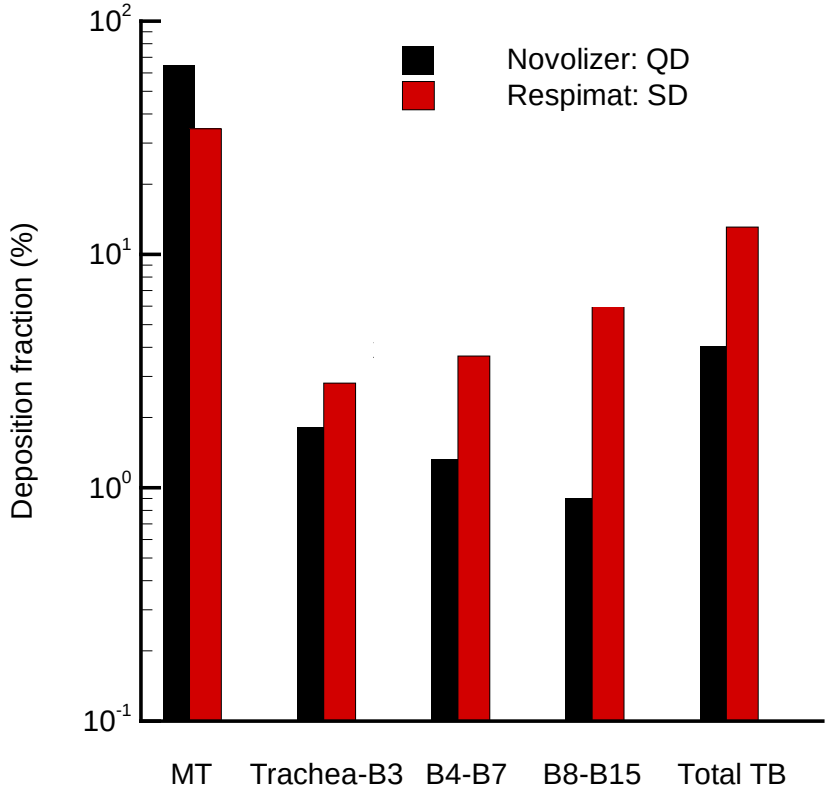
Where does CFD come in?

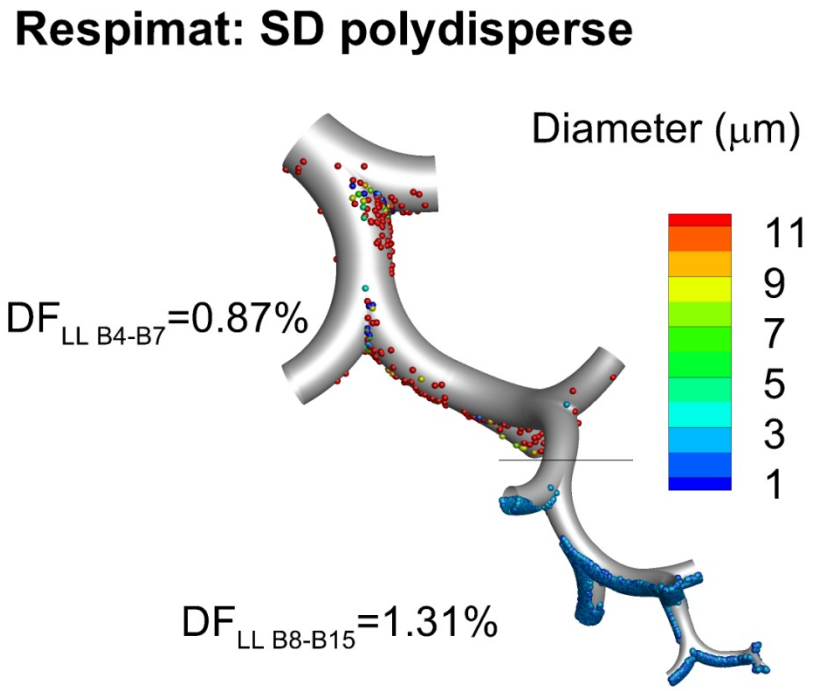
- Coupling careful modeling with *in vitro* testing enables CFD model validation.
  - e.g. Novolizer (75 LPM for 4 s); Respimat at 37 LPM (Medium MT-TB)
- Tian et al. (2012) *Aerosol Sci. Technology* 46, 1271-1285



CFD Models for Regional Distribution

- Based on size distribution of $TLD_{in\ vitro}$ (drug aerosol entering lung) and validated CFD model …. predict regional distribution in lung.
- Tian et al. (2012) *Aerosol Sci. Technology* 46, 1271-1285





Stochastic Individual Pathway model

The Future for Inhaler Comparisons

- Validated "realistic' mouth-throat models (adult human: S, M, L)
- Public database of inhalation profiles
  - Median & CIs for different airflow resistance DPIs
  - "Leaflet training" vs "personal training (Rx)" [VCU in preparation]
  - pMDIs, Gender, age, disease effects needed (*TBD*)
- Use new *in vitro* tests (with *IVIVC*) to compare values for $\boldsymbol{TLD_{in\ vitro}}$
- Measure APSD emitted from MT… or MT-TB models with realistic profiles [use in vitro data from MT-TB to validate CFD model]…*TBD*
- Predict *regional* lung deposition using CFD for realistic breath profiles (noting that CFD is most reliable under the lower Reynold's number conditions typical of lung generations 4 through 23)… *TBD*

- Accepted bio-relevant in vitro tests coupled with CFD predictions
  - Easier bridging
  - Easier "bioequivalence" arguments
  - Improved understanding (QbD) and ↓ testing